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(72) Inventor EDWARD JOHN O'BARA

(54) BROMOPHENOL ISOMERIZATION

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of brominated phenolic compounds having a bromo substituent in a position ortho to the hydroxyl group from other brominated phenolic materials.

Bromination of phenolic compounds in which the para position and at least one ortho position are unsubstituted, usually produces a bromination product rich in the para-bromo-isomer. Thus, it is difficult to obtain an ortho-bromo isomer from these starting materials by any direct practical bromination procedures presently known. This is true, for example, in the bromination of m-cresol, the various meta-substituted xylenols, and other (C_1—C_4) alkyl substituted phenols. For this reason the ortho isomers are relatively expensive and not readily available as intermediates in the manufacture of known products.

One method for obtaining the desired ortho-isomers is to form a bromination product by conventional means, and convert the brominated materials to the desired ortho-isomers. One method of producing ortho-isomers "indirectly" is disclosed in U.S. Patent No. 3,293,309. Therein it is said that 2-bromophenol, 6-bromo-o-cresol and 6-bromo-m-cresol are obtained from the corresponding 4-bromo-isomer by heating the latter at a temperature from 100° to 200°C. in the presence of an acidic catalyst for a period of time sufficient for a substantial degree of isomerization to take place. The acidic catalyst is the hydrogen bromide generated in the bromination step or a Friedel-Crafts catalyst such as $AlCl_3$, $AlBr_3$, $FeCl_3$, and the like, or a combination of two or more of these. Best results are reported with a combination of hydrogen bromide and a non-volatile co-catalyst, preferably phosphoric acid. The difficulty with this process is that isomerization is carried out at high temperatures which results in a relatively high concentration of dibrominated and decomposition products. Moreover, in the case of m-alkyl-phenols, e.g., m-cresol, the isomerization leads to almost equal amounts of the 2-bromo and 6-bromo isomers. Although both isomers are ortho bromo substituted, it is usually desirable to obtain one or the other of these isomers in predominant amounts. The process of the prior art is not satisfactory in such cases. The process is also disadvantageous from the standpoint of the need to handle highly corrosive, hot hydrogen bromide.

In accordance with the present invention, it has been discovered that brominated phenolic compounds containing at least one unsubstituted position ortho to the phenolic hydroxyl group can be isomerized to the desired ortho bromo isomer in good yields by allowing the para bromo isomer to "age" at a relatively low temperature in the presence of an inert solvent and hydrogen bromide. In a further aspect of this invention an unbrominated phenolic material is brominated in the presence of the solvent which is useful during the isomerization and/or disproportionation of the brominated phenolic product to the desired ortho-isomer-rich product.

The process of this invention is distinguished by the fact that the desired conversion (i.e., isomerization and/or disproportionation), and preferably, also the bromination, is conducted in the presence of an inert solvent at relatively low temperatures for a period of time which is sufficient to obtain a higher concentration of the desired ortho bromo isomer. In most cases the maximum ortho content is achieved at equilibrium. However, we have found that the maximum concentration of 6-bromo-m-alkyl-phenols e.g. 6-bromo-m-cresol, occurs at a time prior to equilibrium.

One of the essential features of the process of this invention is the use of an inert solvent in the conversion reaction, and preferably also in the bromination reaction. The solvent permits the attainment of the maximum concentration of the desired ortho isomer in the short-

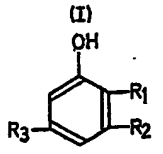
est time at the lowest temperature. In the absence of a solvent the conversion to the ortho isomer occurs, but at a very slow and impractical rate at low temperatures.

The inert solvents of choice are the chlorinated aliphatic and aromatic hydrocarbons and nitro aromatic hydrocarbons. Chloroform is preferred in most instances. Other suitable solvents include chlorinated benzenes, chlorobenzene, carbon tetrachloride, methylene chloride, tetrachloroethylene, nitrobenzene, and combinations of two or more of these solvents. The amount of solvent used in the reaction mixture can be optimally that amount which will result in a high yield of the desired ortho isomer in a desirably short time at about room temperature. In general, this will be at least one part by volume of solvent for each part by weight of the brominated phenolic starting material, and preferably from 5 to 10 parts per part of brominated phenolic starting material, on the same basis.

It has been found that much of the hydrogen bromide generated in the bromination reaction remains in solution and this amount is sufficient to catalyze the conversion to the desired ortho isomers at the temperature envisioned for the process. Although, not necessary to the success of the conversion, additional HBr may be bubbled through the reaction mixture during the interval in which conversion occurs, to maintain a saturated solution of HBr. This latter technique may be desirable when the isomerization and/or disproportionation reaction is conducted at the upper temperatures of the range described below since under these conditions the volatile HBr tends to leave the reaction mixture.

One of the surprising aspects of the process of this invention is that conversion to the ortho isomers occurs and proceeds at a reasonable rate even at low temperatures. Useful results are obtained in the broad range of from −25°C. to 100°C. It is preferred to conduct the isomerization at a temperature in the range of from −25°C. to 60°C., and still more preferably at a temperature in the range of from 20°C. to 30°C.

The present invention is applicable to brominated derivatives of the phenolic compounds of the formula (I):



wherein R_1, R_2 and R_3 are hydrogen or primary or secondary alkyl groups (1—4 carbon atoms). Included among the phenolic compounds described by the above formula are phenol, ortho-cresol, meta-cresol, 2,3-xylenol, 2,5-xylenol, 3,5-xylenol, ortho ethylphenol, meta ethylphenol, ortho propylphenol, ortho isopropylphenol, ortho butylphenol, ortho isobutylphenol, meta propylphenol, meta isopropylphenol, meta butylphenol, beta isobutylphenol, 2,5-diethylphenol, 2,3-diethylphenol and 3,5-diethylphenol.

The brominated phenolic starting materials which are useful in the process of the invention may contain only a single phenolic compound or it may be a mixture of unbrominated, monobromo and/or dibrominated phenolic compounds. The mixtures of phenolic materials can be obtained by simply mixing a brominated phenol with one or more brominated and/or unbrominated phenols, or, more usually, by direct bromination of an unbrominated phenolic material. Depending upon bromination conditions, the bromination mixture can contain a variety of compounds ranging from unbrominated starting material to dibrominated compounds and including various para- and ortho-monobrominated phenolic materials. Bromination should not be allowed to proceed to the point at which two equivalents of bromine have reacted with each equivalent of the phenolic compound. In general, in fact, if the bromination is being conducted for the purpose of producing starting materials for the process of this invention, it is desirable to brominate to the point where between 0.5 and 1.5, and preferably 1 to 1.3, equivalents of bromine per phenolic equivalent are reacted. This will mean that in the reaction product there is only a small amount of unreacted starting material, a minor amount of dibromophenolic materials and a preponderance of mono-brominated material. Such mixtures are eminently suitable for the purposes of this invention.

As has been noted hereinabove, the sources of the brominated phenolic material is not important. Pure materials can be blended to give simulated bromination mixtures or mixtures of brominated derivatives can be formed *in situ*. For example, it is possible to blend a predominantly dibrominated phenol, with an essentially unbrominated phenol, and, by disproportionation, obtain a mixture which has a desirably high ratio of mono-brominated materials.

When the phenolic compounds of formula I are brominated, the bromine atom is directed predominantly to the para position. In the case of m-cresol, e.g., the concentration of the para isomer in the reaction mixture following completion of bromination in the absence of solvent is about 50—55 mole percent, while the concentration of the 2- and 6-isomers totals about 30 mole percent. The same mixtures, after aging to attain essentially equilibrium conditions, contain about 20 mole percent of each of the 2- and 6-isomers and 26 mole percent of the 4-isomer. Though not previously recognized, the concentration of the 6-bromo isomer of m-cresol or other m-alkylphenols is greater

at an intermediate time after bromination, but before equilibrium of the bromination mixture has been achieved.

It has been found that the isomerization of the para bromo phenols proceeds to the equilibrium state in a relatively short time when the reaction is conducted according to this invention. The maximum concentration of the ortho bromo isomer is normally attained at equilibrium. However, it has been discovered that the isomerization of 4-bromo-m-cresol proceeds to equilibrium through an intermediate maximum concentration of the 6-bromo-m-cresol. At equilibrium the 2- and 6-isomers are present in approximately equal concentrations. This intermediate maximum concentration represents about 38% of the 6-bromo-m-cresol after 48 hours at 25°C. when the isomerization is conducted in a solvent consisting of 4 parts of chlorobenzene and one part of carbon tetrachloride. The equilibrium concentration is about 20%. In order to obtain the maximum ortho concentration when this is achieved prior to equilibrium, the isomerization may be terminated at the desired time by drowning the reaction mixture in an alkaline medium, e.g. aqueous sodium hydroxide.

The bromination reaction may be conducted under conventional conditions, preferably using at least a stoichiometric amount of bromine. When stoichiometric quantities of bromine are used, the reaction mixture will usually contain some unreacted phenolic material. For example, when bromo-m-cresol reaction mixture is allowed to stand in the presence of HBr, some of the mono-brominated product is debrominated to m-cresol and bromine. As a result there is an increase in concentration of dibromo isomers (2,4-, 2,6- and 4,6-) by reaction of the bromine with the monobrominated product. Thus, when the desired quantity of the ortho isomer is attained, additional bromine may be added to the reaction mixture to brominate the remaining unbrominated cresol prior to separation of the product.

As noted above, it has also been discovered in accordance with this invention that dibrominated products resulting from the bromination of the phenolic compounds of this invention, specifically the 2,4- and 4,6-dibromo-m-alkylphenols can be converted to the corresponding ortho bromo isomer by disproportionation of a mixture of the dibromo compounds with an unbrominated phenolic compound, preferably an equimolar quantity of the corresponding unbrominated phenolic compound, in the presence of HBr. Thus, a mixture of m-cresol and 2,4-, and 4,6-dibromo-m-cresols can be disproportionated, resulting in the formation of the desired 2-bromo and 6-bromo-m-cresols.

In order to isolate the desired ortho bromo-substituted isomer from the mixture obtained as a result of the aging step according to this invention, the mixture is first neutralized with an alkaline material and the neutralized product is then subjected to a suitable isolation technique. One procedure is to drown the reaction mixture in an alkaline medium eg. aqueous sodium hydroxide, withdraw, and then neutralize with an acid, the aqueous layer containing the phenolic compounds, and separate the product portion which is then distilled *in vacuo* to obtain the ortho bromo isomers. In the case of m-cresol and 2- and 6-bromo isomers have similar boiling points, and are not easily separated by distillation; they may be separated by forming the benzene or paratoluene-sulfonates, separating the sulfonates by crystallization, recrystallizing and finally hydrolyzing the sulfonate to the desired brominated phenolic compound.

The following Tests are presented to further illustrate this invention. In all the tests where pertinent vapor phase chromatographic data are given, the following system was used unless otherwise noted.

Column: 6 ft. 20% "Carbowax" 20M on "Chromosorb" W; 60/80 mesh ("Carbowax" and "Chromosorb" are registered Trade Marks)
Detector: Thermal conductivity
Carrier gas: Helium
Flow rate: 200 ml./min.
Temperature: Injection port—200°C; Block—255°C.
Column: a) 135°C. for separation of 2-bromo-m-cresol, 6-bromo-m-cresol and m-cresol.
b) 175—200°C. for separation of dibromo-m-cresols and 4-bromo-m-cresol from the above.

Samples were treated with sodium carbonate prior to analysis. Peak areas were calculated by the method of triangles and gave mole % directly.

TEST 1.

Bromination and Isomerization of m-Cresol Without Solvent

m-Cresol was brominated according to the procedure of Example 8 of U.S. Patent No. 3,293,309.

m-Cresol was brominated at 55—65°C. with an equivalent of bromine added as a gas carried by a stream of nitrogen. The reaction mixture was then heated to 145—155°C. for 6 hours in the presence of residual hydrogen bromide to determine the extent of isomerization. The mixture was then heated an additional 6 hours at the same temperature after addition of 1% by weight of phosphoric acid and with a stream of hydrogen bromide bubbling through the liquid. The composition in terms of mole percentages of the isomers 1) after the bromination, 2) after the first period of heating and 3) after the addition of phosphoric acid and the second period of heating the mixture saturated with hydrogen bromide, are listed below. Vapor phase chro-

matographic (VPC) analysis of the reaction mixture was compared with the analysis reported in Test 8 of the above cited patent.

TABLE I

Component	Analysis Shown in U.S. 3,293,309			Analysis by VPS		
	(1)	(2)	(3)	(1)	(2)	(3)
m-cresol	5.7	6.4	16.5	9.4	10.5	19.5
2-bromo-m-cresol	—	—	—	7.6	9.2	19.6
6-bromo-m-cresol	32.8	39.5	41.6	22.0	26.0	20.0
4-bromo-m-cresol	51.5	42.3	23.1	53.5	44.5	26.4
4,6-dibromo-m-cresol	10.0	11.5	16.9			
dibromo (2,4 + 4,6) m-cresol	—	—	—	7.5	9.8	14.5
others	—	—	1.9	—	—	—

This test illustrates (a) that the concentration of the 6-isomer does not significantly change in the process whereas the concentration of the 2-isomer is more than doubled, (b) that the state achieved in step (3) is approximately the equilibrium condition, and (c) that the optimum concentration of the 6-isomer is not obtained unless the aging step is of limited duration.

TEST 2.

Bromination of m-Cresol

m-Cresol was brominated at 25°C. in chloroform using a 24% stoichiometric excess of bromine as follows:

20 Grams (0.185 mole) of m-cresol were dissolved in 80 ml. of chloroform. A solution of 36.7 grams (0.229 mole) of bromine in 80 ml. of chloroform was added dropwise to the m-cresol solution over 2 hours at 25°C. The flask was then stoppered and allowed to stand at 25°C.

Analysis of the reaction mixture was made periodically throughout the reaction. These data are shown below in tabular form (Table II).

TABLE II

Bromination of m-Cresol

Variation of Composition with Time, (mole %)

	Time (Hrs.)	m-Cresol	2-bromo	6-Bromo	2- + 6-	di-bromo	4-bromo
Bromination	0	100	0	0	0	0	0
	0.5	63			4.1	4.7	28.2
	1.0	38.5			9.1	4.4	48.0
	1.5	13.6			16.9	9.4	60.0
	2.0	0			22.0	19.2	58.8
Isomerization	0	0	3.2	18.8	22.0	19.2	58.8
	1	4.4			26.5	20.9	48.2
	3	6.2			34.6	24.2	34.6
	5	6.4	8.6	28.8	37.4	24.8	31.5
	8	7.2	12.0	30.2	42.2	23.1	27.6
	22	8.7	20.0	27.8	47.8	22.2	21.2
	140	11.2	19.7	20.2	39.9	31.2	17.7
	266	11.0	20.1	20.7	40.8	28.9	18.8

It is clear from the data that the concentration of the 6-isomer increases from 18.8 mole percent of the reaction mixture after completion of the bromination, to a maximum of 30.2 mole percent after allowing the reaction mixture to stand at 25°C. for 8 hours in the presence of residual hydrogen bromide. Continued isomerization under the same conditions results in a reduction of the 6-isomer content, the entire mixture approaching the equilibrium state. The maximum concentration of the 2-isomer occurs at equilibrium.

TEST 3.

Hydrogen bromide was bubbled through a crude mixture of bromo-m-cresols at 0—5°C. for five minutes. The ice bath was removed and the mixture allowed to warm to room temperature in a stoppered flask. The mixture solidified and was allowed to stand at room temperature for 6 hours and then heated on a steam bath *in vacuo* to liquefy the solid and remove HBr. The liquid was again saturated with HBr and allowed to stand at room temperature for a total of 96 hours. Analysis of the mixtures by vapor phase chromatography showed the following compositions (Table III):

TABLE III

	Mole %			
Aging Time	2- + 6- isomer	m-cresol	Dibromo	4-isomer
After 0	23.2	1.4	16.3	59.1
After 6 hours	22.9	3.0	16.9	57.1
After 96 hours	26.8	12.0	24.1	36.6

This test illustrates the slow rate of increase in ortho-isomer content when the isomerization is conducted in the absence of solvent at a low temperature.

TEST 4.

Bromination of m-Cresol

m-Cresol (20 g., 0.185 mole) was dissolved in a mixture of 80 ml. of chlorobenzene and 20 ml. of carbon tetrachloride. To this solution was added a solution of bromine (29.6 g., 0.185 mole) in 80 ml. of chlorobenzene and 20 ml. of carbon tetrachloride over 6 hours at 25°C. The solution was then allowed to stand at 25°C. in a stoppered flask and samples were removed periodically for VPC analysis with the following results (Table IV):

TABLE IV

	mole %				
Aging time (hrs.)	m-cresol	2-Br	6-Br	dibromo	4-Br
0	5.9	3.6	16.8	2.0	71.6
16	8.2	8.8	33.4	4.1	45.4
24	8.6	9.8	36.7	4.5	40.4
48	9.1	12.8	38.2	5.5	34.4
66	10.0	14.2	38.2	6.0	31.5
138	10.5	17.1	36.3	7.6	28.6

TEST 5.

Isomerization of p-Bromophenol with Hydrogen Bromide

p-Bromophenol (4.63 grams, 0.027 mole) was dissolved in 23 ml. of chloroform. The solution was saturated with anhydrous HBr and allowed to stand at 25°C. in a stoppered flask. Samples were analyzed by VPC.

Time, hrs.	o-Bromo Phenol	Phenol	Dibromophenols	p-Bromophenol
0	0	0	0	100
120	20	6	6	68
483	44	6	8	42
1032	49	7	10	34

This test illustrates the applicability of the process of the invention to phenolic compounds which do not contain a meta-alkyl group.

TEST 6.

Isomerization of 4-Bromo-3,5-Dimethylphenol

4-Bromo-3,5-dimethylphenol (5.43 g., .027 mole) was dissolved in 44 ml, of chloroform. This solution was saturated with anhydrous HBr and allowed to stand at 25°C. in a stoppered flask. Samples were removed periodically for VPC analysis.

Time	3,5-dimethyl phenol	2-bromo-3,5-dimethylphenol	4-bromo-3,5-dimethylphenol	dibromo-3,5-dimethylphenol	
				2.4-	2,6-
0	0.4	—	98.4	1.2	—
5 min.	6.5	54.4	30.9	8.2	—
0.5	7.5	63.7	17.9	10.8	trace
1	8.9	65.8	15.6	9.6	trace
4	9.7	64.3	15.7	9.9	0.5
24	10.2	64.1	14.7	8.6	2.2
48	10.1	61.9	16.0	8.3	3.7
72	10.9	57.2	17.2	9.5	5.1

Column: 6 ft. 10% UC-W98 (Silicone rubber)
Column temperature: 150—200°C., programmed at 6° per min.
Helium flow rate: 150 ml./min.

This test illustrates the applicability of the process of the invention to other phenolic compounds wherein the predominating 4-bromo isomer is isomerized to the desired ortho isomer.

TEST 7.
Isomerization of 4-Bromo-m-Cresol in Nitrobenzene

4-Bromo-m-cresol (5.0 g., 0.027 mole) was dissolved in 23 ml. of nitrobenzene. The solution was saturated with anhydrous HBr and allowed to stand at 25°C. in a stoppered flask. Samples were removed periodically for VPC analysis.

Time hr.	2-bromo-m-cresol	6-bromo-m-cresol	m-cresol	dibromo-m-cresol	4-bromo-m-cresol
0	0	0	0	0	100
4	(1)*		5	5	89
24	2	13	6	6	73
96	8	20	10	10	52
144	(27)*		12	12	49
192	(25)*		13.5	13.5	48
264	(25)*		15	15	45
360	11	14	16	16	44
624	12	13	16	16	43

*Parenthetical values refer to sum of 2-bromo and 6-bromo isomers.

This test illustrates the applicability of the process of the invention in solvents other than chlorinated hydrocarbons; in particular, nitrobenzene.

TEST 8.

Conversion of a Mixture of Dibromo-m-Cresols and m-Cresol

A solution of 5 g. of m-cresol in 20 ml. of chloroform was treated with two equivalents of bromine in 20 ml. of chloroform over a period of 1 hour at 25°C. To this mixture was then added 5 grams of m-cresol in 10 ml. of chloroform, and the mixture allowed to stand in a stoppered flask at 25°C. Samples for VPC analysis were taken (A) after bromination, (B) after adding m-cresol, and (C) periodically during the isomerization.

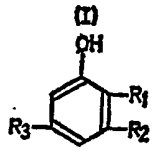
Time hrs.	2-bromo-	6-bromo	m-cresol	2,4- and 4,6-dibromo	4-bromo
(A)	(2)*		0	90	8
(B)	—		49	46	5
3.5	(6)*		41	48	5
21.5	(20)*		35	34	11
46.5	(30)*		28	26	15
93	15 (32)*	17	26	23	19
123	16 (33)*	17	25	22	20
460	21 (42)*	21	22	16	20

*Parenthetical values refer to sum of 2-bromo and 6-bromo isomers.

This test illustrates the applicability of the process of the invention to disproportionated dibrominated - m - cresols/m - cresol mixtures with the resultant preparation of the ortho bromo isomers.

WHAT WE CLAIM IS:—

1. A process for obtaining an ortho bromo-substituted phenol by increasing the ortho bromo content in a brominated phenol material derived from a phenol of formula I:



wherein R_1, R_2 and R_3 are each hydrogen or a primary or secondary (C_1—C_4) alkyl group, said brominated phenol material having a bromine content of less than two atoms of bromine for each phenol nucleus, which process comprises aging a solution of the brominated phenol material in an inert solvent in the presence of hydrogen bromide at a temperature of from −25°C to 100°C for a period of time sufficient to permit the brominated material to isomerize and/or disproportionate whereby the ortho bromo content is increased, treating the resulting mixture of products with an alkaline material whereby isomerization and/or disproportionation is terminated, and separating the desired ortho bromo isomer from the mixture of products thus obtained.

2. A process according to Claim 1, wherein the starting material is a product obtained by brominating a phenol of formula I in said inert solvent.

3. A process according to Claim 1 or Claim 2, wherein the starting material is brominated m-cresol.

4. A process according to Claim 1 or Claim 2, wherein the starting material is brominated xylenol.

5. A process according to Claim 1, wherein the starting material has been formed by mixing a predominantly dibrominated phenol of formula I with a predominantly unbrominated phenol of formula I.

6. A process according to any preceding claim, wherein said inert solvent is a chlorinated hydrocarbon or a nitro aromatic hydrocarbon.

7. A process according to Claim 6, wherein said inert solvent is chloroform, or a mixture of chlorobenzene and carbon tetrachloride.

8. A process according to any preceding claim, wherein said aging is carried out at a temperature of from −25°C to 60°C.

9. A process according to Claim 8, wherein said aging is carried out at a temperature of from 20°C to 30°C.

10. A process for obtaining an ortho bromo-substituted phenol, according to Claim 1 and substantially as hereinbefore described.

11. An ortho bromo-substituted phenol whenever obtained by a process according to any preceding claim.

TREGEAR, THIEMANN & BLEACH,
Chartered Patent Agents,
Melbourne House,
Aldwych,
London, W.C.2.
Agents for the Applicants.

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